

Supplementary Material

Phytoestrogens in Postmenopause: The State of the Art from a Chemical, Pharmacological and Regulatory Perspective

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Table 1S. Details on Published Reviews and Meta-Analyses on Phytoestrogens According to Relevant Diseases. In the Table "+" Indicates a Potential Benefit, "?" an Uncertain Benefit, and "-" no Benefit.

Cardio-Metabolic Disorders					
Reference	Year	intervention	Authors' assessment	Outcome	Main results
Herrington [1]	2000	Phytoestrogens	+	LDL, cholesterol, triglycerides (human) and endothelial-dependent vasodilation (monkeys).	Reduction in LDL, cholesterol and triglycerides levels associated with phytoestrogens may have positive cardiovascular effects.
Glazier [2]	2001	Phytoestrogens	+	VLDL, LDL, HDL, cholesterol serum levels.	Animal and human studies found reduced lipid levels with phytoestrogens.
Ariyo [3]	2002	Phytoestrogens	+	LDL, HDL, cholesterol and triglyceride levels.	Overall, soy phytoestrogens caused significant reductions of cholesterol, LDL and triglyceride level, while increasing HDL levels.
Ewies [4]	2002	Phytoestrogens	+	LDL, HDL, cholesterol and triglyceride levels. Systemic arterial compliance, blood pressure.	Isolavones contributed significantly on the cholesterol-lowering effects of soy protein. Effect of isolavones on blood pressure is likely to be small, but significant improvement of systemic arterial compliance.
Messina [5]	2002	Soybeans	+	Platelet aggregation, LDL levels, systemic arterial compliance.	Soy protein and isolavones either reduce or have no effect on platelet aggregation. Soy protein may actually decrease the gallbladder risk by decreasing liver and biliary cholesterol concentrations. Epidemiological data suggest potential cardioprotective effects of soy.
Phipps [6]	2002	Isolavones	+	LDL, HDL levels, systemic arterial compliance, blood pressure, coagulation and fibrinolytic factors.	The consumption of soy protein, as opposed to animal protein, is beneficial from the standpoint of cardiovascular disorder, both for postmenopausal women and humans in general.
Jacquot [7]	2003	Phytoestrogens	?	Nitric oxide release, thromboxane A2 levels, L-type calcium channels.	There are contradictory data on endothelium-dependent relaxation caused by phytoestrogens.
Altavilla [8]	2004	Genistein	+	Markers of apoptosis, cell differentiation, proliferation, angiogenesis, endothelial nitric oxide, LDL, HDL, brachial artery diameter/blood flow.	In vitro and animal evidence suggest cardio-vascular protective effect of phytoestrogens. Human studies, high amounts of soy proteins appear effective in lowering lipid levels. In humans, genistein clearly improves endothelial vasodilation in post-menopausal women.
McCue [9]	2004	Soy isolavones	+	Cholesterol and LDL levels, blood pressure, platelet aggregation.	Consumption of soy proteins may reduce the risk of coronary heart disease.

Nandur [10]	2004	Phytoestrogens	+	Cholesterol, LDL, HDL and triglyceride levels, systemic arterial compliance, nitric oxide release.	Data suggest modest effect on cardiovascular biomarkers
Cassidy [11]	2006	Phytoestrogens	+	Lipoprotein status and glycaemic indices.	The consumption of whole-soyabean foods and soyabean-protein isolates has some beneficial effects on lipid markers of cardiovascular risk in healthy postmenopausal women. There may be an effect of soyabean on diabetes.
Geller [12]	2006	Isoflavones	+	Cardiovascular risk markers (overall cholesterol, LDL and HDL).	Soy appears to reduce total cholesterol levels and LDL cholesterol, while red clover reduces triglycerides and increases HDL cholesterol.
Usui [13]	2006	Phytoestrogens	+	Cardio-metabolic risk markers (e.g. LDL, HDL, insulin resistance, body weight).	The beneficial effect of phytoestrogens on cardiovascular diseases need to be confirmed. A diet rich in phytoestrogens can have beneficial on many aspects of diabetes and obesity.
Vafeiadou [14]	2006	Isoflavones	-	Cardiovascular risk markers including plasma biomarkers of lipoprotein and glucose metabolism and circulating inflammatory markers (e.g. total cholesterol, HDL-C, triacylglycerol, lipoprotein(a), LDL).	Isoflavone-enriched foods do not have any beneficial effect on markers of lipoprotein and glucose metabolism and cannot improve the concentrations of the majority of circulating inflammatory biomarkers in healthy postmenopausal women.
Cano [15]	2010	Isoflavones	+	Cardiovascular markers (e.g. total cholesterol, LDL, insulin resistance, platelet activation, adhesion molecules).	Both the experimental and the clinical information suggest that the action of isoflavones substantially overlaps with that of estrogens in what refers to cardiovascular disorders.
Ricci [16]	2010	Soy isoflavones	-	Fasting blood glucose changes from baseline.	Soy isoflavones did not affect fasting blood glucose significantly. Difference in fasting blood glucose values between women assigned to isoflavones and women assigned to placebo was -2.16 mg/dL (95% CI, -5.21 to 0.89 mg/dL; P = 0.17).
Aging					
Reference	Year	intervention	Authors' assessment	Outcome	Main results
Li SH [17]	2010	Isoflavones	?	Weighted mean differences (WMD) of endothelial function, measured by flow-mediated dilation (FMD)..	Isoflavone supplementation does not improve endothelial function in postmenopausal women with high baseline FMD levels (WMD: 0.24%; 95% CI: -0.94% to 1.42%; P = 0.69) but leads to significant improvement in women with low baseline FMD levels (WMD: 2.22%; 95% CI: 1.15%, 3.30%; P = 0.0001).
Dong [18]	2011	Soy isoflavones	?	C-reactive protein (CRP) change.	Insufficient evidence that soy isoflavones significantly reduce CRP concentrations (reduction of 0.17 mg/L 95%CI= -0.38 to 0.04; P = 0.12). However, soy isoflavones may produce a significant reduction in CRP among subjects with elevated baseline CRP.
Menopausal Symptoms					
Reference	Year	intervention	Authors' assessment	Outcome	Main results
Glazier [2]	2001	Phytoestrogens	+	Hot flushes and wheat flour.	Statistically significant reduction of hot flushes frequency with phytoestrogens.
Ewies [4]	2002	Phytoestrogens	+	Hot flushes and night sweats.	A statistically significant reduction in hot flushes after a treatment with phytoestrogens was found in different human studies.
Phipps [6]	2002	Isoflavones	?	Hot flushes, genital atrophy.	The use of isoflavones appears, at best, to be only modestly successful in addressing vasomotor symptoms, and provides essentially no benefit for symptoms of genital atrophy.

Jacquot [7]	2003	Phytoestrogens	?	Weakly hot flushes	Contradictory data on effect of phytoestrogens in contrasting hot flushes via nitric oxide synthase stimulation and L-type calcium channels blockade.
Viereck [19]	2005	Actaea racemosa extracts	+	Hot flushes, night sweats.	Statistically significant superiority over placebo has been shown for black cohosh.
Cassidy [11]	2006	Phytoestrogens	+	Hot flushes reduction.	Soybean-isoflavone extracts may be effective in reducing hot flushes.
Howes [20]	2006	Isoflavones	+	Hot flushes reduction.	Isoflavone supplementation was found to be associated with a significant reduction in flushes (effect size -0.28, 95% CI -0.39 to -0.18, P < 0.0001).
Usui [13]	2006	Phytoestrogens	?	Hot flushes reduction.	The results for phytoestrogens are mixed: some studies report a modest benefit compared with placebo and others do not.
Williamson [21]	2011	Isoflavones	?	Hot flushes reduction and modification of circulating hormone levels.	There are a marked variability among results of reviewed studies concerning isoflavones.
Hooper [22]	2009	Soy isoflavones	-	Circulating hormone concentrations (estradiol, estrone, SHBG, FSH and LH).	In post-menopausal women, there were no statistically significant effects of soy isoflavones on estradiol, estrone, SHBG, FSH or LH levels.
Bone Disorders					
Reference	Year	intervention	Authors' assessment	Outcome	Main results
Arjmandi [23]	2001	Phytoestrogens	+	Bone mineral density and other indices of bone turnover (e.g., urinary N-telopeptide).	Based on animal and human evidence, flaxseed, dried plums and prunes may reduce bone loss by enhancing antioxidant status.
Glazier [2]	2001	Phytoestrogens	+	Bone mineral density.	Human studies found beneficial effects of ipriflavone in reducing bone loss.
Ewies [4]	2002	Phytoestrogens	+	Bone mineral density and content.	Decreased rate of bone loss in human studies for ipriflavone.
Messina [5]	2002	Soybeans	+	Bone mineral density and fracture risk, calcium urinary excretion.	Studies in post-menopausal women are generally favourable with effects of soybeans, primarily at the spine.
Phipps [6]	2002	Isoflavones	?	Bone mineral density.	The evidence that isoflavones have clinically important beneficial effects on bone for post-menopausal women is not at all substantial.
Jacquot [7]	2003	Phytoestrogens	?	Osteoblastic and osteoclastic activity.	Hypothesized in vitro osteoblastic stimulatory activity
McCue [9]	2004	Soy isoflavones	+	Bone mass and resorption.	Soybean isoflavonoids have been shown to improve bone mass and reduce bone resorption
Messina [24]	2004	Soy isoflavones	+	Bone mineral density and content.	The analysis of 15 trials overall suggest that isoflavones exert skeletal benefits in younger postmenopausal women (nearly half of the trials demonstrated statistically significant effects). The epidemiologic literature suggests that soy intake is related to higher bone mineral density
Viereck [19]	2005	Actaea racemosa extracts	+	Bone density and bone mineral content, bone metabolic index	Most studies suggest bone-sparing effects of a phytoestrogen-rich diet only after long-term application. Significant superiority of black cohosh over placebo was demonstrated in one study
Cassidy [11]	2006	Phytoestrogens	?	Bone biomarkers and bone density	There is a suggestion, but no conclusive evidence, that isoflavones have a beneficial effect on bone health.

Geller [12]	2006	Isoflavones	+	Bone mineral content (BMC), bone mineral density (BMD), or markers of bone resorption.	Although the evidence is very limited, it appears that red clover and soy isoflavones may have a somewhat helpful effect on bone mineral density in peri- and postmenopausal women.
Usui [13]	2006	Phytoestrogens	?	Bone mass	Soy isoflavones have a modest effect in retarding bone loss
Ricci [25]	2010	Soy isoflavones	-	Lumbar spine bone mineral density (LS-BMD)	The effect of phytoestrogens on LS-BMD was not statistically significant (mean difference 9.86 mg/cm ² , 95% CI -2.64 to 22.36).
SalariSharif [26]	2011	Phytoestrogens	+	Bone resorption biomarkers: changes of pyridinoline (Pyd) and desoxypyridinoline (Dpyd) in urine and serum.	The urine Pyd and Dpyd levels decreased significantly in phytoestrogens consumers. Effect size for Pyd levels showed -1.229171 (95% CI=-1.927639 to -0.530703) and for Dpyd -0.520132 (95% CI=-0.871988 to -0.168275), respectively.
Williamson [21]	2011	Isoflavones	?	Bone resorption marker (urinary deoxypyridinoline) and markers of bone formation (bone alkaline phosphatase and osteocalcin).	Soy isoflavones decreased bone resorption but not bone formation.
Cognitive Disorders					
Reference	Year	intervention	Authors' assessment	Outcome	Main results
Kim [27]	2000	Genistein	+	Cognitive dysfunction, Alzheimer disease	Preliminary experiments showed that isoflavones attenuated neurodegeneration-related modifications in a primate model of menopause
Phipps [6]	2002	Isoflavones	?	Cognitive function	There is very little information on the effects of isoflavones on cognitive function and/or the development of Alzheimer's disease, although such effects are mechanistically plausible
Cassidy [11]	2006	Phytoestrogens	?	Cognitive tests such as verbal memory, digit span (a measure of short-term memory) and verbal fluency.	It is not possible to draw a conclusion on the effect of soyabean products or isoflavones on cognitive function
Geller [12]	2006	Isoflavones	+	Improvements in short-term memory, frontal lobe function, mental flexibility, planning ability, category fluency, and sustained attention.	It appears that soy isoflavones could have positive effects on cognitive function in postmenopausal women; however, more research is needed for both soy and red clover isoflavones.
Usui [13]	2006	Phytoestrogens	?	Risk of Alzheimer disease and dementia.	The effects of phytoestrogens on the central nervous system in humans, especially on learning and memory, are controversial .
Neoplasm prevention					
Reference	Year	intervention	Authors' assessment	Outcome	Main results
Horn-Ross [28]	1995	Phytoestrogens	+	Postmenopausal breast cancer risk	Based on ecologic, experimental, and epidemiologic evidence, the consumption of phytoestrogens may inversely relate to the risk of breast cancer by attenuating the effects of adiposity
Glazier [2]	2001	Phytoestrogens	?	Cell growth (in vitro), tumour size (animal), lobular epithelial growth and urinary excretion (human).	Pre-clinical data suggest antineoplastic activity, but conflicting clinical evidence
Ewies [4]	2002	Phytoestrogens	+	Cancer cell growth (in vitro), tumour size (animal), cancer occurrence (human).	Potential chemopreventive effect of Asian diet

Lord [29]	2002	Lignans	+	Sex hormone binding protein, tumour growth, tumour biomarkers, 2-16 α ratios between hydroxymetabolites	In vitro and in vivo studies showed potential chemopreventive properties by increasing removing endogenous estrogens. Human studies showed that pre- and postmenopausal women with urinary 2/16 α ratios above 2.0 have reduced risk for estrogen-sensitive cancers
Messina [5]	2002	Soybeans	+	Breast cancer density.	Soy either has no effect on or decreases breast cancer risk.
Phipps [6]	2002	Isoflavones	?	Breast and endometrial cancer risk.	Essentially complete lack of direct evidence in decreasing the risk of breast and endometrial cancer.
Jacquot [7]	2003	Phytoestrogens	?	Breast cancer risk.	Phytoestrogens caused a decrease in the apparition of estrogenic and non-estrogenic molecules, but data are inconsistent.
Limer [30]	2004	Phytoestrogens	+	Breast cancer incidence, proliferation of breast epithelia, growth inhibition.	Rodent studies suggest that soy products may possess antitumour activities. Short-term studies suggest an association between phytoestrogen consumption and a favourable steroid hormone profile.
McCue [9]	2004	Soy isoflavones	+	Apoptosis pathways (e.g., p53, caspase-3 activation, down-regulation of BCL-2, activation of Nf-kB).	In vitro studies found chemo-protective properties associated with soybean foods.
Gikas [31]	2005	Phytoestrogens	?	Breast cancer risk, mammographic densities.	There is no clear evidence that phytoestrogen intake influences the risk of developing breast cancer.
Mahady [32]	2005	Soy isoflavones	+	Endometrial cancer risk, endometrial hyperplasia.	Epidemiological studies suggest that isoflavones may actually reduce the risk of cancer rather than increase it.
Viereck [19]	2005	Actaea racemosa extracts	-	Breast cancer risk, tumour growth.	None prospective clinical trials showed a significant protective effect of phytoestrogens.
Cassidy [11]	2006	Phytoestrogens	?	Mammographic density as a marker of breast cancer risk. Colo-rectal cancer risk.	There is some epidemiological evidence of an association between lifelong soybean intake and reduced risk of breast cancer. No general support for the hypothesis that frequent ingestion of soybean reduces the risk of colo-rectal cancer.
Qin [33]	2006	Soy isoflavones	+	Breast cancer risk.	The pooled RR of breast cancer for soyfood intake was 0.75 with s 95% CI of 0.59-0.95.
Usui [13]	2006	Phytoestrogens	?	Breast cancer risk and endometrial cancer risk.	The overall clinical and epidemiological information on phytoestrogens and breast cancer risk are still scarce. Few studies showed a reduction of endometrial cancer risk with some phytoestrogen compounds.
Duffy [34]	2007	Phytoestrogens	-	Breast cancer risk and markers of breast cancer.	There is very little human data on the role of phytoestrogens in preventing breast cancer recurrence, but the few studies conducted do not support a protective role.
Messina [35]	2008	Soy isoflavones	?	Breast proliferation, mammographic density and breast cancer risk.	There are no data to support the idea that soyfoods or isoflavone supplements improve the prognosis of breast cancer patients.
Velentzis [36]	2009	Lignans	+	Breast cancer risk.	Lignans may be associated with a small reduction in post-menopausal breast cancer risk. In particular, high levels lignan intake were associated with reduced breast cancer risk (OR: 0.85, 95% CI: 0.78-0.93).
Buck [37]	2010	Lignans	+	Breast cancer risk.	High lignan intake was associated with a significant reduced risk of breast cancer (pooled risk estimate: 0.86; 95%CI: 0.78-0.94).

Hooper [38]	2010	Isoflavones	?	Breast density.	Isoflavones had no effect on breast density in post-menopausal women and a small effect in premenopausal women.
Zaineddin [39]	2012	Lignans	+	Breast cancer risk.	Breast cancer risk decreased with increasing serum enterolactone levels (OR: 0.65; 95% CI: 0.52–0.83).

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Table 2S. PICO (Patient/Population, Intervention, Comparison and Outcome) of RCTs of Phytoestrogens Published in the Last 5 Years

Ref	Year	Patient/Population	Intervention	Comparison	Outcome
Okamura [1]	2008	Postmenopausal women with insufficient oestrogens	Oral administration of <i>Pueraria mirifica</i> powder	Placebo	Serum lipid parameters (HDL, LDL, apo-A, apo-B)
Chedraui [2]	2008	Postmenopausal women with increased body mass index	80 mg red clover (isoflavones) daily for a 90-day	Placebo	Lipid profile total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C) and lipoprotein A (LpA)
Verheus [3]	2008	postmenopausal women ages 60 to 75 years	soy protein intake containing 99 mg isoflavones daily for 1 year	Placebo (milk protein)	Mammographic density
Rios [4]	2008	Postmenopausal women 47-66 years	40 mg of isoflavones	Placebo	Cardiovascular risk factors (lipid profile)
Aubertin-Leheudre [5]	2008	Obese postmenopausal women	6 months of isoflavone supplement (70 mg)	Placebo	Cardiovascular disease (CVD) risk factors
Törmälä [6]	2008	Postmenopausal women on tibolone treatment	52 g of soy protein containing 112 mg of isoflavones	Placebo	Effects of soy on sex steroids and vascular inflammation markers
Appt [7]	2008	Postmenopausal women on tibolone treatment	52 g of soy protein containing 112 mg isoflavones daily for 8 weeks	Placebo	Effect on lipids (LDL, HDL)
Nasca [8]	2008	Healthy postmenopausal women	Diet in which 0.5 cups of soy nuts (25 g soy protein and 101 mg aglycone isoflavones)	Placebo (therapeutic lifestyle change diet)	Markers of inflammation
Atteritano [9]	2008	Postmenopausal women	Genistein (54 mg/day) for 1 year	Placebo	Cytogenetic biomarkers
Hallund [10]	2008	Healthy postmenopausal women	Daily a low-fat muffin, with a lignan complex, for 6 weeks	Placebo	Inflammation markers (C-reactive protein)
Pop [11]	2008	Healthy postmenopausal women	Soy isoflavones administered daily for 84 days	Placebo	DNA damage, apoptosis, and oestrogenic outcomes
Marini [12]	2008	Osteopenic postmenopausal women	Genistein, (n = 198; 54 mg/d)+ Vit D for 2 years	Placebo + Vit D	Bone turnover (serum levels of both soluble RANKL and OPG and the sRANKL/OPG ratio)
Jou [13]	2008	Healthy menopausal women	35 mg of isoflavones daily for 1 week	Placebo	Menopausal symptoms were evaluated using a modified Kupperman Index
Powles [14]	2008	Women with a family history of breast cancer	40 mg red clover isoflavone for 3 years	Placebo	Prevention of breast cancer
Brink [15]	2008	Healthy early postmenopausal women	Mean daily intake of 110 mg isoflavone aglycones for 1 year	Placebo	Bone mineral density of the lumbar spine and total body, markers of bone formation and bone resorption
Manonai [16]	2008	Healthy postmenopausal women aged 45 to 60 years old	20, 30, or 50 mg <i>Pueraria mirifica</i> in capsules once daily for 24 weeks	Placebo	Lipid profiles, bone-specific alkaline phosphatase level, endometrial thickness, endometrial histology, breast ultrasonography, complete blood count, liver function test, and renal function test
Rios [17]	2008	Postmenopausal women	40 mg of soy isoflavone once a day for	Placebo	Effects of isoflavones on the coagu-

Ref	Year	Patient/Population	Intervention	Comparison	Outcome
			6 months		lation and fibrinolytic system
Törmälä [18]	2008	Women using tibolone for 3-60 months	Soy drink (52 g of soy protein containing 112 mg of isoflavones) for 8 weeks	Placebo	Vascular function (Arterial stiffness and endothelial function)
Greany [19]	2008	Postmenopausal women	Soy protein isolate (26+/-5 g protein containing 44+/-8 mg isoflavones per day) for 6 weeks	Placebo (milk protein)	Markers of inflammation (Concentrations of Hcy, CRP, sE-selectin, sVCAM-1 and sICAM-1)
Terzic [20]	2009	Healthy postmenopausal women with an average age of 56 years	Red clover-derived isoflavone medication	Placebo	Total blood cholesterol, cholesterol fractions and triglycerides
Beavers [21]	2009	Postmenopausal women	3 servings of vanilla soy per day for 4 weeks	Placebo (reduced fat dairy milk)	Plasma markers of inflammation (tumor necrosis factor alpha [TNF-alpha], interleukin [IL]-1beta, IL-6) and oxidative stress (superoxide dismutase [SOD], glutathione peroxidase [GPx], cyclooxygenase-2 [COX-2])
Wong [22]	2009	Postmenopausal women	80 or 120 mg of soy hypocotyl aglycone isoflavones plus calcium and vitamin D	Placebo	Changes in whole-body and regional bone mineral density (BMD), bone mineral content (BMC), and T scores were assessed
Maki [23]	2009	Midlife women with 35 or more weekly hot flashes	Red clover (120 mg), black cohosh (128 mg), 0.625 mg conjugated equine oestrogens plus 2.5 mg medroxyprogesterone acetate (CEE/MPA)	Placebo	Cognitive function
Moraes [24]	2009	Postmenopausal women	Topical administration of isoflavones 40% (genistein 4%) on facial skin for 24 weeks	Topical administration of beta-oestradiol (0.01%) on facial skin for 24 weeks	Skin morphological parameters
Basaria [25]	2009	Healthy, ambulatory, post-menopausal women	20 g of soy protein containing 160 mg of total isoflavones	Placebo	Self-reported quality of life (QOL), cognition, lipoproteins and androgen status
Maskarinec [26]	2009	Postmenopausal women	80 or 120 mg/d of isoflavones for 2 years	Placebo	Mammographic density
D'Anna [27]	2009	Postmenopausal women	Phytoestrogen genistein	Placebo	Reductions from the baseline in the frequency and severity of hot flashes
Villa [28]	2009	Postmenopausal women	54 mg/d genistein for 24 weeks	Placebo	Cardiovascular risk factors (Anthropometric measures, hormonal and lipid assays, oral glucose tolerance test)
Charles [29]	2009	Healthy postmenopausal women	20 g of soy protein with 160 mg of total isoflavones (64 mg genistein, 63 mg daidzein, and 34 mg glycitein) for 12 weeks	Placebo	Metabolic and inflammatory markers (glucose, insulin, and adipokines/cytokines)
Del Giorno [30]	2010	Women aged 45-65 years with menopausal symptoms	40 mg Trifolium pratense, 1 capsule/day for 12 months	Placebo	Kupperman Menopausal Index and the Golombok Rust Inventory of Sexual Satisfaction (GRISS) were used
Bitto [31]	2010	Osteopenic, postmenopausal women	54 mg of genistein aglycone daily plus calcium and vitamin D(3) at therapeutic	Placebo + calcium and vitamin D(3)	Serum thyroid hormones or autoantibodies

Ref	Year	Patient/Population	Intervention	Comparison	Outcome
			doses		
Liu [32]	2010	Postmenopausal Hong Kong Chinese women with prediabetes or early untreated diabetes	15 g soy protein and 100 mg isoflavones, 15 g milk protein and 100 mg isoflavones for 6 months	Placebo (15 g milk protein on a daily basis for 6 mo)	Glycaemic control and insulin resistance
Llaneza [33]	2010	Postmenopausal women with insulin resistance	Mediterranean diet, physical exercise, and daily oral ingestion of 40 mg of soy isoflavones	Mediterranean diet and physical exercise	Anthropometric measures, Kupperman Index values, Cervantes Scale score, and blood samples for glucose, insulin, lipid profile, creatinine, uric acid, homocysteine, folic acid, vitamin B12, selenium, and oestradiol
Campbell [34]	2010	Hypercholesterolemic postmenopausal women	Soy or daily for 1 year	Placebo	Heart disease risk. Serum samples were analyzed for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, apolipoprotein (Apo) A, and Apo B
Matvienko [35]	2010	Healthy postmenopausal women	Soy isoflavone (80 or 120 mg/d) tablets for 12 months	Placebo	Changes in body composition (whole-body lean mass, whole-body fat mass, android fat mass, and androidal-to-gynoidal fat mass ratio) and appetitive hormones (insulin, leptin, ghrelin, and adiponectin)
Lipovac [36]	2010	Postmenopausal women aged 40 or more	Two daily capsules of 80mg red clover isoflavones	Placebo	Anxiety and depressive symptoms with the Hospital Anxiety and Depression Scale (HADS) and Zung's Self Rating Depression Scale (SDS)
Simbalista [37]	2010	Women who had been postmenopausal for 1-10 y	2 slices of bread containing 25 g of flaxseed (46 mg lignans) every day for 12 consecutive weeks	Wheat bran (<1 mg lignans; control) every day for 12 consecutive weeks	Daily number of hot flashes, the Kupperman Menopausal Index (KMI), and endometrial thickness.
Liu [38]	2010	Postmenopausal Chinese women with mild hyperglycemia	15 g soy protein and 100 mg isoflavones (Soy group), or 15 g milk protein and 100 mg isoflavones (Iso group), on a daily basis for 6 months	15 g milk protein (placebo group) on a daily basis for 6 months	Changes of body weight (BW), body mass index,
Alekel [39]	2010	Healthy postmenopausal women (aged 45.8-65.0 y)	2 soy isoflavone groups (80 compared with 120 mg/d)	Placebo	Lumbar spine, total proximal femur, femoral neck, and whole-body BMD
Gobert [40]	2010	Adults with diet-controlled type 2 diabetes	Soya protein isolate (SPI) and milk protein isolate (MPI) for 57 d each separated by a 4-weeks washout	Placebo	Glycaemic control
Marini [41]	2010	Postmenopausal women with low bone mass for 24 months	54 mg of genistein aglycone daily + calcium and vitamin D(3)	Placebo + calcium and vitamin D(3)	Blood lipid profiles, fasting glucose and insulin, insulin resistance (HOMA-IR), fibrinogen, osteoprotegerin (OPG) and homocysteine were measured
Hodis [42]	2011	Postmenopausal women 45 to 92 years of age without diabetes and cardiovascular disease	Daily doses of 25 g soy protein containing 91 mg aglycon isoflavone equivalents for 2.7 years	Placebo	Subclinical atherosclerosis assessed as carotid artery intima-media thickness progression.

Ref	Year	Patient/Population	Intervention	Comparison	Outcome
Riesco [43]	2011	Postmenopausal women	Phytoestrogen supplements	Placebo	Body weight, fat mass and lean body mass were assessed. Quality of life was estimated by the Short Form-36 (SF-36) and Perceived Stress Scale-10 (PSS-10) questionnaires, and menopausal symptoms by the Kupperman index
Wang [44]	2011	Healthy postmenopausal women	Diet supplemented with soy food (SFD; 50 mg isoflavones per day)	Diet with no soy food	Potential of gene expression profiling in peripheral blood mononuclear cells
Gossell-Williams [45]	2011	Women who had undergone natural menopause or had iatrogenically entered the climacteric due to surgery for benign pathology	Pumpkin seed oil	Placebo	Serum lipids, fasting plasma glucose and blood pressure
Tousen [46]	2011	Non-equol-producing menopausal Japanese women	2 mg of equol supplement per day, 6 mg of equol supplement per day, and 10 mg of equol supplement per day	Placebo	Effects of equol on bone metabolism and serum sex and thyroid hormone levels
Choquette [47]	2011	Obese postmenopausal women	Isoflavones (70 mg/d of isoflavones), exercise and isoflavones	Placebo, exercise and placebo	Fat mass (FM), lean body mass (LBM), bone mineral density, lipid profile, fasting glucose, fasting insulin and insulin resistance
Steinberg [48]	2011	Healthy postmenopausal women	80 or 120 mg aglycone equivalent soy hypocotyl isoflavones plus calcium and vitamin D	Placebo	Blood lymphocyte or serum free thyroxine concentrations, endometrial thickness or fibroids.
Evans [49]	2011	Postmenopausal women	Single 30 mg dose of synthetic genistein	Placebo	Percentage change in the number of daily hot flushes from pre-treatment to week 12
Llaneza [50]	2011	Healthy obese postmenopausal women	1200 kcal diet, exercise, and daily oral intake of daily oral intake of a soy isoflavones extract (Fisiogen®) contained 200 mg of Glycine max, which corresponded to 80 mg of isoflavone (60.8 mg of genistein, 16 mg of daidzein and 3.2 mg of glicitein)	1200 kcal diet and exercise group	Anthropometric measures, body composition, leptin, adiponectin, TNF-alpha, homocysteine, C-reactive protein, glucose, insulin, lipid profile and oestradiol serum levels, Kupperman index and Cervantes Scale
Hachul [51]	2011	postmenopausal women with insomnia	80 mg isoflavones daily for 4 months	Placebo	Sleep analysis consisted of questionnaires and polysomnography
Le Donne [52]	2011	Postmenopausal women	Intravaginally 97 µg of genistein daily for 15 days continuously/month for 3 months	Intravaginally 5 mg of hyaluronic acid daily for 15 days continuously/month for 3 months	Vaginal and cervical smear, colposcopy, vaginal biopsy were performed
Henderson [53]	2012	Healthy postmenopausal women	Soy isoflavone tablets, 200 mg	Placebo	Changes in bone mineral density
Jenks [54]	2012	Postmenopausal women (aged 45-65 years), who experienced ≥5 hot flashes/day	Soy isoflavones	10, 20, or 40 mg S-equol/day	Reductions in hot flash frequency
Tedeschi [55]	2012	Menopausal women with vaginal dystrophy	Gel containing isoflavones for 4 weeks + daily oral isoflavones	No topical treatment + daily oral isoflavones	Severity of itching, burning, vulvovaginal erythema, vaginal dryness and dyspareunia

Ref	Year	Patient/Population	Intervention	Comparison	Outcome
Wong [56]	2012	Hypercholesterolemic men and postmenopausal women	Soy foods with high-normal (73 mg/d) isoflavones	Soy foods with low (10 mg/d) isoflavones	Variation in LDL and HDL cholesterol levels
Ye [57]	2012	Postmenopausal Chinese women, aged 45 to 60 years	Daily doses of 84, and 126 mg of soy germ isoflavones	Placebo	Hot flush frequency, Kupperman scores, serum 17 β -oestradiol, follicle-stimulating hormone, luteinizing hormone, and serum lipids
Curtis [58]	2012	Postmenopausal women with type 2 diabetes	27 g/day (split dose) flavonoid-enriched chocolate (containing 850 mg flavan-3-ols [90 mg epicatechin] and 100 mg isoflavones [aglycone equivalents]/day) 1 year.	Placebo	Variation in insulin, HDL and LDL levels
Lee [59]	2012	Healthy postmenopausal women aged 68 \pm 7 who were not receiving hormonal replacement therapy	0.05 mg or 0.1 mg transdermal oestrogen/day	40 or 80 mg oral phytoestrogen/day	Insulin sensitivity
Oyama [60]	2012	Postmenopausal Japanese women who were equol nonproducers	10 mg S-equol/day, or 30 mg S-equol/day	Placebo	Skin parameters of crow's-feet wrinkles (area and depth), hydration, transepidermal water loss, and elasticity
Lipovac [61]	2012	Postmenopausal women aged 40 or more	Two daily capsules of 80 mg red clover isoflavones	Placebo	Daily hot flush and night sweat frequency and overall menopausal symptom intensity (Kupperman Index)
Riesco [62]	2012	Obese women aged between 50 and 70 years	Exercise with phytoestrogens	Exercise with placebo	Body weight, waist circumference, fat mass, and lean body mass

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